Claims 72-89 and 100-106 are currently pending in the application, claims 103-106 having been newly added. Of these claims, 78,79, 82, 89 and 102 have been withdrawn from consideration by the Examiner as being drawn to a non-elected invention and/or species. A clean copy of the specification, page 1, as now amended and a clean copy of the claims currently pending, as amended, are appended hereto for the Examiner's convenience.

Amendments to claims

Claims 103-106 are new. Support for the term "artificial amino acids" used in claim 103 is found in the specification on page 15, lines 15-20. Support for the term "β-alanine" used in claim 104 is also found in the specification on page 15, lines 15-20. Support for the term "amino or thiol side groups" used in claim 105 is found in the specification on page 9, lines 9-12. Support for the term "peptidic nucleic acids" recited in claim 106 is found in the specification on page 7, lines 6-22.

Rejection under 35 USC §102 (b) (Examiner's paragraphs 14 and 15)

The Examiner has maintained the rejection of claims 72-77, 80-81, 83-88 and 100-102 (formerly directed to claims 72, 74-77, 80-81, 83 and 86) under 35 USC §102 (b) as being anticipated by Bredehorst *et al.* (*Analytical Biochemistry 193*:2, 272-279, 1991, hereinafter "Bredehorst"). The Examiner's position is that Bredehorst teaches insulin (a polymeric carrier having 21 amino acids) conjugated to a dinitrophenol (DNP) group and three fluorescein molecules coupled to reactive side groups (carboxyl or amine) at predetermined positions, and that therefore, Bredehorst anticipates the invention of claims 72, 74-77 and 80-81. The Examiner further argues that, as the carrier has negatively charged sulfate groups, it anticipates claim 83, and as the molecular weight of DNP is in the range of 100-2000 daltons, claim 86 is anticipated. (Note: Applicants note that the Examiner has included claim 102 in the rejection; however, they also note that claim 102 has been withdrawn from consideration by the Examiner.)

Previously, Applicants argued in their Amendment and Reply of February 15, 2001 that claim 72, which had been amended to recite the limitation " the carrier is non-immunologically reactive when the monomeric units are amino acids", was now distinguished over the prior art. The Examiner found this argument unpersuasive in light of the new matter rejections set forth under the New Grounds of Rejection section of the office action (paragraph no. 21). Applicants have below traversed the Examiner's new matter rejection, and Applicants now repeat their argument that the prior art does not teach or suggest Applicants' invention wherein the synthetic polymeric carrier comprising the conjugate is non-immunologically reactive when the monomeric units are amino acids. Based upon their arguments against the new matter rejection and the restated arguments above, Applicants now submit that the Examiner's rejection under 35 USC §102 (b) has now been overcome, and they respectfully request the Examiner's reconsideration of the rejection of claims 72-77, 80-81, 83-88 and 100-102.

Rejection under 35 USC §103 (a) (Examiner's paragraph 16)

The Examiner has maintained the rejection of claims 72-77, 80-81, 83-88 and 100-101 (formerly directed to claims 72, 74-77, 80-81, 83 and 86) under 35 USC §103 (a) as being unpatentable over Bredehorst in view of US Patent No. 5,310,687 to Bard *et al.*, (hereinafter "Bard"). The Examiner's position is that Bredehorst teaches insulin (a polymeric carrier having 21 amino acids) conjugated to a dinitrophenol (DNP) group and three fluorescein molecules coupled to reactive side groups (carboxyl or amine) at predetermined positions. The carrier has negatively charged sulfate groups, and the molecular weight of DNP is in the range of 100-2000 daltons. Bredehorst does not teach the use of luminescent metal chelates as a marker with superior properties for use in assays. The Examiner argues that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the luminescent metal chelates of Bard in the conjugates as taught by Bredehorst because Bredehorst teaches the incorporation of detectable marker groups into conjugates for immunoassays, and Bard teaches the incorporation of luminescent metal chelates into molecules for detecting

analytes in immunoassay formats. The Examiner further argues that one of ordinary skill in the art would have been motivated to make the combination and would reasonably have been expected to be successful based upon the teachings of Bredehorst and Bard.

Applicants argue that, even if one skilled in the art were motivated to combine the luminescent metal chelate of Bard with the amino acid carrier molecule of Bredehorst, the present invention is still not achieved. Neither Bredehorst nor Bard teaches or suggests the non-immunologically reactive amino acid backbone carrier of the present invention. Further, neither Bredehorst nor Bard teaches the nucleotide or nucleotide analogue carrier of the present invention. In the Bard reference, only the use of immunologically reactive peptides as a carrier for luminescence labeled metal complexes is taught. A conjugate wherein the amino acid backbone merely serves for the presentation of the immunologically reactive haptens and the labeling group or solid phase binding group is neither disclosed nor rendered obvious. Applicants' position is that the examiner's *prima facie* case of obviousness has not been made, and they respectfully request the Examiner's reconsideration of the rejection of claims 72-77, 80-81, 83-88 and 100-101 under 35 USC §103 (a).

Rejection under 35 USC §103 (a) (Examiner's paragraphs 17 and 18)

The examiner has maintained the rejection of claims 72-77, 80-81, 83-88 and 100-101 (formerly directed to claims 72, 74-77, 80-81, 83 and 86) under 35 USC §103 (a) as being unpatentable over PCT application WO 92/20703 to Buchardt *et al.* (hereinafter "Buchardt") in view of Bredehorst. The Examiner's position is that Buchardt teaches the synthesis and use of peptide nucleic acids (PNA, which reads on nucleotide analogs and amino acids as each monomeric unit of a PNA is an amino acid) wherein the PNA is made of at least 2 monomers and wherein the length is from 2-61. Buchardt teaches that PNA molecules may be conjugated to reporter ligands which read on marker groups, haptens or solid phase binding groups coupled to reactive side chains.

Buchardt does not explicitly recite incorporating both marker groups and haptens or solid phase binding groups into a single polymeric conjugate molecule.

Bredehorst teaches an insulin A-chain backbone with a hapten and a marker group both incorporated along the backbone. There is no teaching in either Bredehorst or Buchardt, however, of how one would incorporate both haptens and marker groups on the backbone of Buchardt, or how one would incorporate the hapten and marker groups of Bredehorst on the PNA backbone taught by Buchardt. Bredehorst does not teach the use of protecting groups having different functions in the same molecule, as insulin A-chain has a defined sequence of 21 amino acids with one amino functionality and three carboxyl functionalities exactly 4, 17 and 21 amino acids away from the terminal amino, the site used for hapten coupling. Only the teachings of the present invention describe how to construct an amino acid backbone with predetermined sites for attachment of haptens and marker groups, and only the teachings of the present invention describe the incorporation of multiple hapten groups along the same backbone. The examiner's *prima facie* case of obviousness has not been made, and Applicants respectfully request the examiner's reconsideration of her rejection.

Rejection under 35 USC §103 (a) (Examiner's paragraph 19)

The examiner has rejected claims 72-77, 80-81 and 83-88 under 35 USC §103 (a) as being unpatentable over Buchardt in view of Bredehorst and further in view of Bard.

The Examiner's arguments regarding the teachings of Buchardt in view of Bredehorst are set forth in the preceding rejection. The Examiner argues that Buchardt in view of Bredehorst does not teach the use of luminescent metal chelates as required in an alternative embodiment in claim 81, or as a specific limitation of claims 73 and 84. However, Bard teaches the use of luminescent metal chelates as a marker with superior properties for use in assays. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the luminescent metal chelates of

Bard in the conjugates as taught by Buchardt in view of Bredehorst because Buchardt in view of Bredehorst teaches the incorporation of marker groups into conjugates for immunoassays, and Bard teaches the incorporation of luminescent metal chelates into molecules for detecting analytes in immunoassay formats. The Examiner's position is that Applicants' previous arguments have been considered but found unpersuasive in light of the new matter rejections set forth under the New Grounds of Rejection section of the office action (paragraph no. 21). Applicants have below traversed the Examiner's new matter rejection, and Applicants again argue that the three prior art references, even when combined, still do not give Applicants' invention wherein the synthetic polymeric carrier comprising the conjugate is non-immunologically reactive when the monomeric units are amino acids. Bredehorst has been argued above. In the Bard reference, only the use of immunologically reactive peptides as a carrier for luminescence labeled metal complexes is taught. A conjugate wherein the amino acid backbone merely serves for the presentation of the immunologically reactive haptens and the labeling group or solid phase binding group is neither disclosed nor rendered obvious. Similarly, in Buchardt, the "polymeric carrier" per se is the determining reagent and not the pendant hapten molecules. Applicants again argue that the *prima facie* case of obviousness has not been made. Based upon their arguments against the new matter rejection and the restated arguments above, Applicants now submit that the Examiner's rejection under 35 USC §103 (a) has now been overcome, and they respectfully request the Examiner's reconsideration of the rejection of claims 72-77, 80-81, 83-88.

Rejection under 35 USC §112, first paragraph (Examiner's paragraph 21)

The examiner has rejected claims 72, 82-83 and 100 under 35 USC §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s) had possession of the claimed invention, i.e., as being new matter. (Note: Applicants believe the rejection is intended for claims 83-84 rather than 82-83 and are responding accordingly.) The Examiner has requested that Applicants specifically point out support

for amendments made to the disclosure. The Examiner's position is that the following added material in several amended claims is not supported by the original disclosure:

[1] "wherein the carrier is non-immunologically reactive when the monomeric units are amino acids," i.e., claim 72

[2] "a charged group selected from the group consisting of positively charged groups and negatively charged groups," i.e., claims 83 and 84, and

[3] "wherein the reactive side groups coupling the hapten molecules and the reactive side groups coupling the marker groups or solid phase binding groups are alike," i.e., claim 101.

With respect to the language recited in paragraph [1] above, Applicants direct the Examiner's attention to the specification on page 16, lines 2-7, which reads as follows:

> "The peptide backbone of the conjugate has a non-immunologically reactive amino acid sequence i.e. an amino acid sequence which does not interfere with the test procedure in the intended application of the conjugate as an antigen in an immunological method of detection."

With respect to the language recited in paragraph [2] above, Applicants direct the Examiner's attention to the specification on page 11, lines 4-10, which reads as follows:

> "When using a luminescent metal complex which is detectable by an electrochemiluminescence reaction as the marker group, the incorporation of at least one positive or/and negative charge carrier e.g. amino or carboxylate groups into the carrier chain or/and the spacer between metal complex and carrier chain has proven to be advantageous."

With respect to the language recited in paragraph [3] above, Applicants direct the Examiner's attention to Example 3 in the specification, specifically, page 26, lines 9-11, which reads as follows:

> "The metal chelate and hapten molecules are in each case coupled to the peptide chain via the ε-amino side group of the lysines."

In Example 3, conjugates I and II described therein contain estradiol as hapten and ruthenium conjugate as marker groups, each coupled to the ε-amino side group of the lysine side chain.

Having now pointed out adequate support in the original specification for the amended language in Examiner's paragraphs [1], [2] and [3] above, Applicants respectfully request the Examiner's reconsideration of her rejection of claims 72, 82-83 and 100 under 35 USC §112, first paragraph.

Rejection under 35 USC §112, first paragraph (Examiner's paragraph 23)

Claims 100-101 have been rejected under 35 USC §112, first paragraph, because the specification, while being enabling for a conjugate comprising:

[a] a synthetic polymeric carrier of "a polyamide backbone made of the same or different monomeric units of the formula $(CH_2)_k$–CHR'–N[CO–$(CH_2)_i$–L]–CH_2–$(CH_2)_m$–NH–CO– having a maximum of 100 monomeric units selected from the group consisting of nucleotides and amino acids;

[b] 1-10 hapten molecules;

[c] 1-10 marker groups; or

[d] solid phase binding groups

[e] coupled to reactive side groups

[f] at predetermined positions on the polymeric carrier,

does not provide enablement for all conjugates comprising all synthetic polymeric carriers, all hapten molecules, all marker groups, all solid phase binding groups, coupled to all reactive side groups at all predetermined positions on the polymeric carrier. The specification does not enable any person skilled in the art to practice the invention commensurate in scope with these claims. The Examiner's position is that one skilled in the art could not practice the claimed invention without undue experimentation, as claims

100 and 101 "fail to correlate reasonably with either the enabling disclosure of the specification and the claims."

Applicants respectfully traverse the Examiner's rejection and argue that the skilled artisan is fully enabled by the teachings of Applicants' specification to make any desired conjugate in accordance with Applicants' invention for use as an antigen in an immunological method for determination of antibodies or for DNA diagnostics. Applicants' have disclosed a simple and efficient method for producing such improved antigens, a method which enables selective and reproducible introduction of haptens and marker or solid phase binding groups onto a polymeric carrier. Applicants teach preferred monomeric units, how many monomeric units should preferably comprise the conjugate backbone, how to select the distance between marker groups, how to select the hapten, how to select the marker or solid phase binding groups, *inter alia*. Applicant provides specific examples describing the preparation and incorporation into an amino acid sequence of a metal chelate label and biotin groups. Further disclosed are specific examples describing how to introduce the haptens estradiol and testosterone into the peptide sequence. Then Applicants teach by specific example how to measure estradiol in serum via a competitive immunoassay using a conjugate prepared according to the invention. Depending upon his specific needs, the skilled artisan is already in possession of any additional knowledge that might be required to prepare, without the requirement for undue experimentation, other conjugates in accordance with the present invention. The process used to prepare the conjugates is very specific and very predictable, as the conjugates are made-to-order according to the needs and requirements of the individual artisan.

Applicants having now set forth their position, they respectfully request the Examiner's reconsideration of the rejection of claims 100 and 101 under 35 USC §112, first paragraph.

Rejection under 35 USC §112, second paragraph (Examiner's paragraph 25)

Claim 72 has been rejected under 35 USC §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention. The Examiner argues that claim 72 is vague and indefinite in that the following terms are not defined: "wherein the carrier is non-immunologically reactive when the monomeric units are amino acids." The Examiner's position is that it is unclear what the aforementioned term refers to, as the metes and bounds of the aforementioned claim cannot be determined as the specification, claims and art do not recognize what the generic term "non-immunologically reactive" defines. The Examiner has requested that Applicants point to where in the specification that term is defined, and she requests clarification.

Applicants direct the Examiner's attention to the specification on page 16, lines 2-7, which teaches as follows:

> "The peptide backbone of the conjugate has a non-immunologically reactive amino acid sequence i.e. an amino acid sequence which does not interfere with the test procedure in the intended application of the conjugate as an antigen in an immunological method of detection."

The specification clearly teaches that a "non-immunologically reactive amino acid sequence" is one that does not interfere with the intended use of the conjugate as an antigen in an immunological detection method. It is well-known to those skilled in the art to which the present invention belongs at the time the invention was made that, in an immunoassay method of a biological sample, the artisan would risk undesirable cross reactions from antibodies present in the sample by introducing naturally-occurring peptide sequences.

Having now pointed out in the original specification where "non-immunologically reactive" is defined, Applicants respectfully request the Examiner's reconsideration of her rejection of claim 72 under 35 USC §112, second paragraph.

Rejection under 35 USC §112, second paragraph (Examiner's paragraph 26)

Claim 100 has been rejected under 35 USC §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention. The Examiner argues that claim 100 is vague and indefinite in that the following terms are not defined: "the conjugate containing 2-10 hapten molecules and 1-10 marker groups or solid phase binding groups, wherein the hapten molecules and the marker groups or solid phase binding groups are coupled to reactive side groups at predetermined positions on the polymeric carrier." The Examiner's position is that it is unclear what the aforementioned term refers to, as the metes and bounds of the aforementioned claim cannot be determined as the specification, claims and art do not recognize what the generic term "predetermined positions on the polymeric carrier" refers to, and/or the meaning of the phrase "2-10 hapten molecules and 1-10 marker groups or solid phase binding groups." The Examiner has requested that Applicants point to where in the specification that term is defined, and she requests clarification.

Applicants traverse the rejection and direct the Examiner's attention to the specification on page 12, lines 1-5, which teaches as follows:

> "...during the synthesis monomer derivatives are introduced at predetermined positions on the carrier which are covalently coupled to hapten molecules or/and marker or solid phase binding groups..."

Applicants argue that those skilled in the art to which the present invention belongs at the time the invention was made would understand that "predetermined" positions refers to positions determined prior to synthesis.

With respect to the phrase "2-10 hapten molecules and 1-10 marker groups or solid phase binding groups," Applicants clarify that this means "2-10 hapten molecules and 1-10 marker groups or solid phase binding groups," i.e., "marker groups" and "solid phase binding groups" are essentially equivalent in that either may be used in

combination with hapten molecules to meet the requirements of the claim. As taught in the specification, on page 7, lines 28-30:

> "The conjugate contains 1-10 hapten molecules preferably 1-6 hapten molecules and especially preferably 1 or 2 hapten molecules."

The specification at page 9, lines 1-3, continues to teach:

> "Moreover the conjugate according to the invention contains 1-10 preferably 2-8 marker or solid phase binding groups."

Having now pointed out in the original specification where "predetermined positions on the polymeric carrier" is defined and where "2-10 hapten molecules and 1-10 marker groups or solid phase binding groups" is clarified, Applicants respectfully request the Examiner's reconsideration of her rejection of claim 100 under 35 USC §112, second paragraph.

Rejection under 35 USC §112, second paragraph (Examiner's paragraph 27)

Claim 101 has been rejected under 35 USC §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention. The Examiner argues that claim 101 is vague and indefinite in that the following terms are not defined: "the conjugate containing 1-10 hapten molecules and 1-10 marker groups or solid phase binding groups, wherein the hapten molecules and the marker groups or solid phase binding groups are coupled to reactive side groups at predetermined positions on the polymeric carrier and wherein the reactive side groups coupling the hapten molecules and the reactive side groups coupling groups or solid phase binding groups are alike." The Examiner's position is that it is unclear what the aforementioned term refers to, as the metes and bounds of the aforementioned claim cannot be determined as the specification, claims and art do not recognize what the generic term "predetermined positions on the polymeric carrier" refers to, what the meaning is of the phrase "1-10 hapten molecules and 1-10 marker groups or solid phase binding groups," and/or what determines that reactive side groups coupling

the hapten molecules and the reactive side groups coupling groups or solid phase binding groups "are alike." The Examiner has requested that Applicants point to where in the specification that term is defined, and she requests clarification. (Note: The Examiner's rejection recited a range of hapten groups for claim 101 as 2-10, but Applicants believe that this was probably a typographical error, and thus Applicants have gone ahead and made the change in the above characterization of the Examiner's rejection.)

Applicants traverse the rejection and direct the Examiner's attention first to the specification on page 12, lines 1-5, which teaches as follows:

> "...during the synthesis monomer derivatives are introduced at predetermined positions on the carrier which are covalently coupled to hapten molecules or/and marker or solid phase binding groups..."

Applicants argue that those skilled in the art to which the present invention belongs at the time the invention was made would understand that "predetermined" positions refers to positions determined prior to synthesis.

With respect to the phrase "1-10 hapten molecules and 1-10 marker groups or solid phase binding groups," Applicants clarify that this means "1-10 hapten molecules and 1-10 marker groups or solid phase binding groups," i.e., "marker groups" and "solid phase binding groups" are essentially equivalent in that either may be used in combination with hapten molecules to meet the requirements of the claim. As taught in the specification, on page 7, lines 28-30:

> "The conjugate contains 1-10 hapten molecules preferably 1-6 hapten molecules and especially preferably 1 or 2 hapten molecules."

The specification at page 9, lines 1-3, continues to teach:

> "Moreover the conjugate according to the invention contains 1-10 preferably 2-8 marker or solid phase binding groups."

With regard to what determines that reactive side groups coupling the hapten and reactive side groups coupling marker or solid phase binding groups are "alike," Applicants refer to the same example used by the Examiner, i.e., Example 3 in the specification. In particular, page 26, lines 9-11, reads as follows:

> "The metal chelate and hapten molecules are in each case coupled to the peptide chain via the ε-amino side group of the lysines."

In Example 3, conjugates I and II described therein contain estradiol as hapten and ruthenium conjugate as marker groups, each of which is coupled to the amino side group of the lysine side chain. If two things are "alike", then one is "like" the other, i.e., one amino side group is considered to be the same as another amino side group, i.e., "alike," whereas an amino group would be "different" than a thiol group. If Applicants have misunderstood this part of this rejection, clarification from the Examiner is requested.

Having now pointed out in the original specification where "predetermined positions on the polymeric carrier" is defined, where "1-10 hapten molecules and 1-10 marker groups or solid phase binding groups" is clarified, and what determines that reactive side groups coupling the hapten and reactive side groups coupling marker or solid phase binding groups are "alike," Applicants respectfully request the Examiner's reconsideration of her rejection of claim 101 under 35 USC §112, second paragraph.

Objection to specification (Examiner's paragraph 29)

The Examiner has objected to the specification because a reference to the prior application must be inserted as the first sentence of the specification of the application if Applicants intend to rely on the filing date of the prior application under 35 USC §119 (e) or §120. Appropriate correction has been requested.

In response to the objection, Applicants have amended the specification by inserting a section with appropriate citations to related applications. The specification

now having been appropriately corrected, the Examiner's reconsideration of the objection to the specification is respectfully requested by Applicants.

Rejection under 35 USC §112, first paragraph (Examiner's paragraph 30)

Claims 72 and 87 have been rejected under 35 USC §112, first paragraph, because the specification, while being enabling for a conjugate comprising:

[g] a synthetic polymeric carrier of "a polyamide backbone made of the same or different monomeric units of the formula $(CH_2)_k$–CHR'–N[CO–$(CH_2)_i$–L]–CH_2–$(CH_2)_m$–NH–CO– having a maximum of 100 monomeric units selected from the group consisting of nucleotides and amino acids;

[h] 1-10 hapten molecules;

[i] 1-10 marker groups; or

[j] solid phase binding groups

[k] coupled to reactive side groups

[l] at predetermined positions on the polymeric carrier; and

[m] the conjugate as in claim 86, wherein the hapten molecules are pharmacologically active substances,

does not reasonably provide enablement for all conjugates comprising: all synthetic polymeric carriers, all hapten molecules, all marker groups, all solid phase binding groups, coupled to all reactive side groups at all predetermined positions on the polymeric carrier and/or all pharmacologically active substances. The specification does not enable any person skilled in the art to practice the invention commensurate in scope with these claims. The Examiner's position is that one skilled in the art could not practice the claimed invention without undue experimentation, as claims 72 and 87 "fail to correlate reasonably with either the enabling disclosure of the specification and the claims."

Applicants respectfully traverse the Examiner's rejection and argue that the skilled artisan is fully enabled by the teachings of Applicants' specification to make any desired conjugate in accordance with Applicants' invention for use as an antigen in an immunological method for determination of antibodies or for DNA diagnostics. Applicants' have disclosed a simple and efficient method for producing such improved antigens, a method which enables selective and reproducible introduction of haptens and marker or solid phase binding groups onto a polymeric carrier. Applicants teach preferred monomeric units, how many monomeric units should preferably comprise the conjugate backbone, how to select the distance between marker groups, how to select the hapten, how to select the marker or solid phase binding groups, *inter alia*. Applicant provides specific examples describing the preparation and incorporation into an amino acid sequence of a metal chelate label and biotin groups. Further disclosed are specific examples describing how to introduce the haptens estradiol and testosterone into the peptide sequence. Then Applicants teach by specific example how to measure estradiol in serum via a competitive immunoassay using a conjugate prepared according to the invention. Depending upon his specific needs, the skilled artisan is already in possession of any additional knowledge that might be required to prepare, without the requirement for undue experimentation, other conjugates in accordance with the present invention. The process used to prepare the conjugates is very specific and very predictable, as the conjugates are made-to-order according to the needs and requirements of the individual artisan.

Applicants having now set forth their position, they respectfully request the Examiner's reconsideration of the rejection of claims 72 and 87 under 35 USC §112, first paragraph.

Rejection under 35 USC §112, second paragraph (Examiner's paragraphs 31 and 32)

Claim 72 has been rejected under 35 USC §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

Applicants regard as their invention. The Examiner argues that claim 72 is vague and indefinite in that the following terms are not defined: "the conjugate containing 1-10 hapten molecules and 1-10 marker groups or solid phase binding groups, wherein the hapten molecules and the marker groups or solid phase binding groups are coupled to reactive side groups at predetermined positions on the polymeric carrier." The Examiner's position is that it is unclear what the aforementioned term refers to, as the metes and bounds of the aforementioned claim cannot be determined as the specification, claims and art do not recognize what the generic term "predetermined positions on the polymeric carrier" refers to, and/or the meaning of the phrase "1-10 hapten molecules and 1-10 marker groups or solid phase binding groups." The Examiner has requested that Applicants point to where in the specification that term is defined, and she requests clarification.

Applicants traverse the rejection and direct the Examiner's attention to the specification on page 12, lines 1-5, which teaches as follows:

> "...during the synthesis monomer derivatives are introduced at predetermined positions on the carrier which are covalently coupled to hapten molecules or/and marker or solid phase binding groups..."

Applicants argue that those skilled in the art to which the present invention belongs at the time the invention was made would understand that "predetermined" positions refers to positions determined prior to synthesis.

With respect to the phrase "2-10 hapten molecules and 1-10 marker groups or solid phase binding groups," Applicants clarify that this means "2-10 hapten molecules and 1-10 marker groups or solid phase binding groups," i.e., "marker groups" and "solid phase binding groups" are essentially equivalent in that either may be used in combination with hapten molecules to meet the requirements of the claim. As taught in the specification, on page 7, lines 28-30:

"The conjugate contains 1-10 hapten molecules preferably 1-6 hapten molecules and especially preferably 1 or 2 hapten molecules."

The specification at page 9, lines 1-3, continues to teach:

"Moreover the conjugate according to the invention contains 1-10 preferably 2-8 marker or solid phase binding groups."

Having now pointed out in the original specification where "predetermined positions on the polymeric carrier" is defined and where "2-10 hapten molecules and 1-10 marker groups or solid phase binding groups" is clarified, Applicants respectfully request the Examiner's reconsideration of her rejection of claim 100 under 35 USC §112, second paragraph.

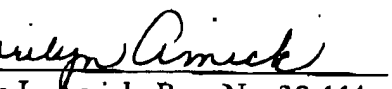
* * * * * *

Applicants submit that their application is now in condition for allowance, and favorable reconsideration of their application in light of the above amendments and remarks is respectfully requested. Allowance of claims 72-77, 80-81, 83-88, and 100-102 at an early date is earnestly solicited.

The Examiner is hereby authorized to charge any fees associated with this Amendment to Deposit Account No. 50-0877. A duplicate copy of this sheet is enclosed.

Respectfully submitted,

November 7, 2001



Marilyn L. Amick, Reg. No. 30,444
Roche Diagnostics Corporation
9115 Hague Road
Indianapolis, IN 46250-0457
Phone: 317-521-7561
Fax: 317-521-2883

Oligomeric carrier molecules with defined inc rp rated marker groups and haptens

RELATED APPLICATIONS

This application is related to PCT/EP 95 Application Serial No. 02915, filed July 24, 1995, from which it derives priority as a US §371 application, and the following foreign applications: Federal Republic of Germany Applications No. P 4426276.0 filed July 25, 1994, P 4430998.8 filed August 31, 1994, P 4430973.2 filed August 31, 1994 and P 4439345.8 filed November 4, 1994, from which it derives priority.

DESCRIPTION

The present invention concerns new conjugates, processes for their production as well as the use of these conjugates as antigens in immunological methods of detection or for DNA diagnostics.

The detection of immunoglobulins in body fluids, in particular in human sera, is used to diagnose infections with microorganisms, in particular viruses, such as HIV, hepatitis viruses etc. The presence of specific immunoglobulins in the examined sample is usually detected by reaction with one or several antigens that react with the specific immunoglobulins. Methods for the determination of specific immunoglobulins in the sample liquid must be sensitive, reliable, simple and rapid.

A further immunological method is a competitive immunoassay in which an analyte is detected qualitatively and quantitatively in such a way that a hapten that is immunologically analogous to the analyte and the analyte compete for binding sites on a receptor e.g. an antibody. The analyte analogue is in this case usually used in a labelled form or in a form capable of binding to a solid phase.

In recent years more and more detection systems based on

72. A conjugate comprising a synthetic polymeric carrier having a maximum of 100 monomeric units selected from the group consisting of nucleotides and amino acids, the conjugate containing 1-10 hapten molecules and 1-10 marker groups or solid phase binding groups, wherein the hapten molecules and the marker groups or solid phase binding groups are coupled to reactive side groups at predetermined positions on the polymeric carrier and wherein the carrier is non-immunologically reactive when the monomeric units are amino acids.

73. The conjugate as claimed in claim 72, wherein the monomeric units are amino acids and the conjugate contains marker groups which are luminescent metal chelates.

74. The conjugate as claimed in claim 72, wherein the polymeric carrier has 3-80 monomeric units.

75. The conjugate as claimed in claim 72, wherein the polymeric carrier has 5-60 monomeric units.

76. The conjugate as claimed in claim 72, wherein the conjugate contains 1-6 hapten molecules.

77. The conjugate as claimed in claim 72, wherein the conjugate contains 2-8 marker groups or solid phase binding groups.

80. The conjugate as claimed in claim 72, wherein the reactive side groups are at least one of reactive amino side groups and reactive thiol side groups.

81. The conjugate as claimed in claim 72, wherein the conjugate contains marker groups which are selected from the group consisting of luminescent metal chelates and fluorescent groups.

83. The conjugate as claimed in claim 72, wherein the polymeric carrier contains a charged group selected from the group consisting of positively charged groups and negatively charged groups.

84. The conjugate as claimed in claim 81, wherein the marker groups are luminescent metal chelates and the polymeric carrier contains a charged group selected from the group consisting of positively charged groups and negatively charged groups.

85. The conjugate as claim in claim 81, wherein the marker groups are fluorescent groups and the polymeric carrier has a helical structure.

86. The conjugate as claimed in claim 72, wherein each of the hapten molecules is an immunologically reactive molecule having a molecular mass of 100-2000 Daltons.

87. The conjugate as claimed in claim 86, wherein the hapten molecules are selected from the group consisting of pharmacologically active substances, hormones, vitamins and neurotransmitters.

88. The conjugate as claimed in claim 72, wherein the hapten molecules are immunologically reactive peptide epitopes having a length of up to 30 amino acids.

100. A conjugate comprising a synthetic polymeric carrier having a maximum of 100 monomeric units selected from the group consisting of nucleotides and amino acids, the conjugate containing 2-10 hapten molecules and 1-10 marker groups or solid phase binding groups, wherein the hapten molecules and the marker groups or solid phase binding groups are coupled to reactive side groups at predetermined positions on the polymeric carrier.

101. A conjugate comprising a synthetic polymeric carrier having a maximum of 100 monomeric units selected from the group consisting of nucleotides and amino acids, the conjugate containing 1-10 hapten molecules and 1-10 marker groups or solid phase binding groups, wherein the hapten molecules and the marker groups or solid phase binding groups are coupled to reactive side groups at predetermined positions on the polymeric carrier and wherein the reactive side groups coupling the hapten molecules and the reactive side groups coupling the marker groups or solid phase binding groups are alike.

103. A conjugate comprising:

a synthetic polymeric carrier comprising a maximum of 100 amino acid monomeric units, the amino acids at least partially comprising artificial amino acids,

1-10 hapten molecules coupled to reactive side groups at predetermined positions on the polymeric carrier, and

1-10 marker groups or solid phase binding groups coupled to reactive side groups at predetermined positions on the polymeric carrier,

wherein the carrier is non-immunologically reactive.

104. The conjugate of claim 103, wherein the artificial amino acids comprise β-alanine.

105. A conjugate comprising:

a synthetic polymeric carrier comprising a maximum of 100 amino acid monomeric units,

1-10 hapten molecules coupled to reactive side groups at predetermined positions on the polymeric carrier, and

1-10 marker groups or solid phase binding groups coupled to reactive side groups at predetermined positions on the polymeric carrier,

wherein the reactive side groups are amino or thiol side groups of the carrier and wherein the carrier is non-immunologically reactive.

106. A conjugate comprising:

a synthetic polymeric carrier comprising a maximum of 100 monomeric units selected from the group consisting of amino acids, nucleotides and peptidic nucleic acids,

1-10 hapten molecules coupled to reactive side groups at predetermined positions on the polymeric carrier, and

1-10 marker groups or solid phase binding groups coupled to reactive side groups at predetermined positions on the polymeric carrier,

wherein the carrier is non-immunologically reactive when the monomeric units are amino acids.